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Strong influence of the trifluoromethyl group on the chemoselectivity of [3+2]-cycloadditions of thiocarbonyl *S*-methanides with α,β-unsaturated ketones

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Keywords: Fluorinated enones, Thiocarbonyl ylides, [3+2]-Cycloaddition, Sulfur heterocycles, Chemoselectivity, Regioselectivity

ABSTRACT

The in situ-generated reactive thiocarbonyl *S*-methanides were reacted with fluorinated enones. The type of the obtained [3+2]-cycloadduct depends strongly on the location of the activating CF_3 group. In the case of enones containing the $CF_3CH=CH$ moiety, the [3+2]-cycloaddition occurs chemo- and regioselectively onto the C=C bond to give trifluoromethylated tetrahydrothiophene derivatives. On the other hand, enones containing the CF_3–C=O unit react as carbonyl dipolarophiles leading to trifluoromethylated 1,3-oxathiolanes also in a chemo- and regioselective manner. These are the first reported reactions of thiocarbonyl *S*-methanides with α,β-unsaturated ketones.

1. Introduction

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Thiocarbonyl *S*-methanides **1** belong to the class of electron-rich S-centered 1,3-dipoles, with have been studied extensively in the last two decades [1]. They cannot be isolated but are generated in situ, preferably by thermal decomposition of corresponding 2,2-disubstituted 1,3,4-thiadiazolines. In the presence of a suitable dipolarophile, they undergo [3+2]-cycloaddition leading to diverse five-membered sulphur hererocycles. In addition, some ethylenic dipolarophiles, activated by strongly electron-withdrawing substituents (e.g. CF_3, C≡N, CO_2R), react with thiocarbonyl *S*-methanides via a stepwise mechanism with a zwitterionic intermediate to give also seven-membered sulfur heterocycles [2].

In general, electron-deficient dipolarophiles are the preferred reaction partners for [3+2]-cycloadditions of **1**, and α,β-unsaturated ketones are well known as active dieno- and dipolarophiles. However, their reactions with thiocarbonyl *S*-methanides have not been reported to date.

Due to our ongoing interest in the development of methods for the preparation of fluorinated heterocyclic compounds, α,β-unsaturated ketones of types **2** and **3**, bearing a CF_3 group, were prepared and tested as dipolarophiles in reactions with in situ-generated aromatic and cycloaliphatic thiocarbonyl *S*-methanides. Up to know, fluorinated α,β-unsaturated ketones have widely been applied for the synthesis of fluorinated heterocycles with diverse ring size, but their reaction with 1,3-dipoles, leading to 5-membered heterocyclic products, are very little known [3a].

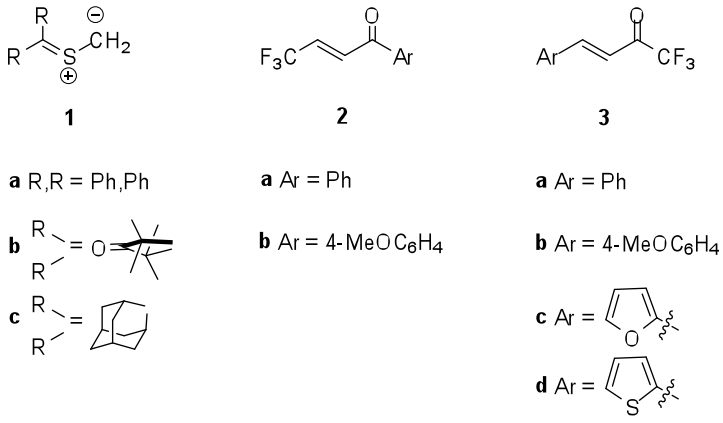


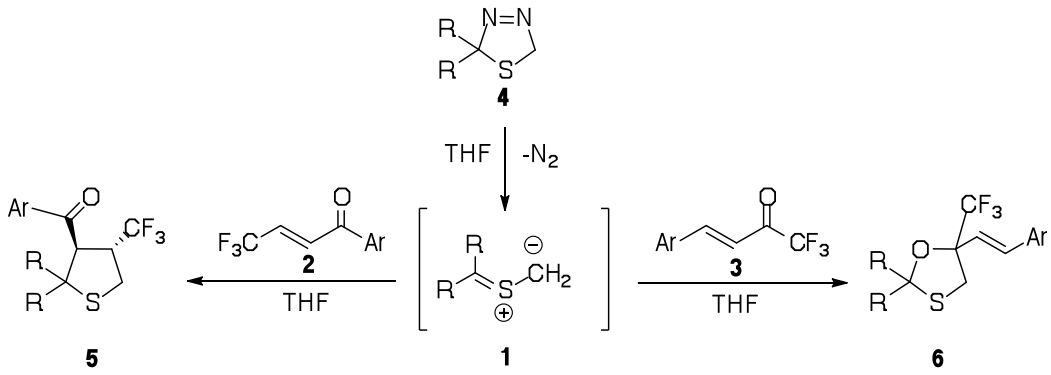
Fig. 1. Stuctures of thiocarbonyl *S*-methanides **1** and α,β-unsaturated ketones **2** and **3**.

2. Results and discussion

The fluorinated α,β-unsaturated ketones **2** and **3** are attractive building blocks for the preparation of more complex fluorinated organic compounds, mainly via heterocyclization

reactions, e.g. with hydrazine and its derivatives [3b–c]. The synthesis of 1-aryl-4,4,4-trifluorobut-2-en-1-ones **2** was described recently [4a–c], starting with 2-bromo-3,3,3-trifluoropropene, which in the first step is treated with LDA, and the formed acetylide reacts with an aromatic aldehyde. Subsequent reduction of the C≡C group and oxidation of the intermediate allyl alcohol lead to chalcones **2**. In general, derivatives **2** are little known compounds and only few examples of their applications have been reported. On the other hand, the 4-aryl-1,1,1-trifluorobut-3-en-2-ones **3** are easily available via aldol condensation of trifluoroacetone and aryl or hetaryl aldehydes, and they have been widely applied in organic synthesis, including [3+2]-cycloadditions with selected diazo compounds [5].

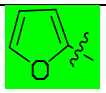
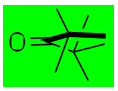
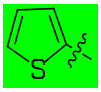
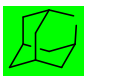
The precursor of thiobenzophenone *S*-methanide (**1a**), i.e. 2,2-diphenyl-1,3,4-thiadiazoline **4a**, was prepared from thiobenzophenone and diazomethane in THF at –70 °C, and after addition of an equivalent amount of the α,β-unsaturated ketone **2a**, the mixture was warmed to –40 °C. At this temperature, elimination of N_2 starts and the reactive **1a** was generated and trapped by the dipolarophile **2a**. The ^{1}H NMR analysis of the crude mixture indicated the formation of a single product, which was identified as tetrahydrothiophene derivative **5a** (Scheme 1, Table 1). Characteristic signals in the ^{1}H NMR spectrum attributed to the $H_2C(5)$ group are two doublet × doublet at 2.87 and 3.16 ppm with $^2J_{H,H}$ = 12.0 Hz and $^3J_{H,H}$ = 10.2 and 7.8 Hz, respectively. Two others signals at 4.15–4.24 ppm (m) and 5.15 (d, $^3J_{H,H}$ = 7.2 Hz) were assigned to HC(4) and HC(3), respectively. The coupling constant $^3J_{H,H}$ = 7.2 Hz for HC(3) (4.2 Hz in **5b** and **5c**, 6.0 in **5d**) can be attributed to the *trans*-configuration in this series of tetrahydrothiophenes **5**. This conclusion is based on the assumption that 1,3-dipolar cycloadditions of thiocarbonyl ylides of type **1** with C=C dipolarophiles containing two vicinal electron-withdrawing groups occur under retention of the configuration [2b, 6]. In general, coupling constants $^3J_{H(3),H(4)}$ in tetrahydrothiophenes of type **5** are with limited diagnostic value for determination of configuration along the C(3)–C(4) bond. A strong IR absorption localized at 1690 cm^{-1} confirmed the presence of the benzoyl group. The regioselective formation of **5a** results from the preferred orientation of the nucleophilic terminus of **1a**, i.e. CH_2, toward the β-position of the Michael-type dipolarophile **2a**.



Scheme 1. Reactions of thiocarbonyl *S*-methanides **1** with fluorinated α,β-unsaturated ketones **2** and **3**.

Table 1

Formation of trifluoromethylated tetrahydrothiophenes **5** and 1,3-oxathiolanes **6** in reactions of thiocarbonyl *S*-methanides with α,β-unsaturated ketones **2** and **3**.

1	R, R	**2**	Ar	**5**	Yield [%][a)]	**3**	Ar	**6**	Yield [%] [a)]
a	Ph,Ph	**a**	Ph	**a**	51	**c**		**a**	59
b		**a**	Ph	**b**	66	**a**	Ph	**b**	78
		b	4-MeOC$_6$H$_4$	**c**	83	**b**	4-MeOC$_6$H$_4$	**c**	69
						d		**d**	87
c		**b**	4-MeOC$_6$H$_4$	**d**	60	**b**	4-MeOC$_6$H$_4$	**e**	66

a) Yield of isolated products, calculated with respect to the enone **2** or **3**.

The cycloaliphatic thiocarbonyl *S*-methanides **1b** and **1c** were generated in situ by heating of the precursors **4b** and **4c**, respectively, in THF at 45 °C in the presence of an enone **2**. In each experiment, only one product was formed and identified as an analogue of **5a** (Table 1).

The reactivity of enones of type **3** was tested in the reaction of **3a** with **1b** using equimolar amounts of **3a** and **4b**. After completion of the N_2-evolution, the analysis of the

crude mixture showed that, along with a new product, substantial amounts of **3a** were still present. In addition, the thiirane formed via electrocyclic ring closure of **1b** [6a] was present in the mixture in ca. 25%. This result points out that the reactivity of enones **3** is reduced in comparison with those of the isomers **2**. Therefore, **3** and **4** were used in a molar ration of 1:1.1.

The IR spectrum of the product obtained from the ylide **1b** and the enone **3a** evidenced the absence of a carbonyl group. On the other hand, the elemental analysis and the mass spectrum confirmed that the product is a 1:1 adduct of **1b** and **3a**. In the ^{1}H NMR spectrum, along with four signals for the methyl groups (1.22, 1.30, 1.35 and 1.40 ppm), two doublets at 6.22 and 6.92 ($^{3}J_{H,H}$ = 16.2 Hz) revealed the presence of a styryl residue. In addition, an AB-system at 3.19 and 3.45 ppm with $^{2}J_{H,H}$ = 12.0 Hz is a typical pattern for the CH_2 unit in five-membered cycloadducts of thiocarbonyl *S*-methanides [7]. Based on these data, the structure of the product was formulated as 1,3-oxathiolane **6b**. An additional support for this structure was the ^{13}C NMR absorption at 102.9 ppm, which is characteristic for C(2) in 1,3-oxathiolanes and related systems [8]. In all experiments with enones of type **3** and thiocarbonyl *S*-methanides **1**, 1,3-oxathiolans **6** were obtained as the only products formed via the [3+2]-cycloaddition. Their structures were provided by the spectroscopic data, which correlated well with those discussed for **6c**.

These results are in line with earlier reports on [3+2]-cycloadditions of diverse 1,3-dipoles with ketones, which are, in general, poor dipolarophiles, and only activation by one or two electron-withdrawing groups attached to the C=O function allow a smooth formation of the five-membered cycloadducts [7,9].

3. Conclusions

The presented study showed that the activation of α,β-unsaturated ketones by the electron-withdrawing CF_3 group enables the [3+2]-cycloadditions with electron-rich thiocarbonyl *S*-methanides. However, depending on the location of the CF_3 group, the reactive dipolarophilic part of the enones is either the C=C or the C=O group. The activated C=C bond in enones **2** reacts as exclusive dipolarophile, whereas in enones **3** the activated C=O group is the more reactive π-system for the [3+2]-cycloaddition reaction with thiocarbonyl *S*-methanides. Furthermore, the experiments evidenced that enones **2** are potent dipolarophiles, which efficiently trap the in situ-generated *S*-methanides **1** without formation of any side products such as thiiranes or 1,4-dithianes. The reported results indicate that fluorinated enones both of

type **2** and **3** can be considered as attractive dipolarophiles for further exploration in [3+2]-cycloadditions with diverse 1,3-dipoles leading to fluoroalkylated, 5-membered heterocycles.

4. Experimental

4.1. General information

Melting points were determined on a Mel-Temp II apparatus (Aldrich) in capillaries, and they are uncorrected. The ^{1}H, ^{13}C{^{1}H} and ^{19}F NMR spectra were recorded on Bruker Avance III 600 or Varian Gemini BB 200 spectrometers using solvent signals as reference. Assignments of signals in ^{13}C NMR spectra were made on the basis of HMQC experiments. The IR spectra were measured using an NEXUS FT-IR spectrophotometer. HR-ESI-MS were recorded on a Bruker maxis spectrometer in the laboratory of Mass spectrometry at the University of Zurich. Elemental analyses were performed in the Microanalytical Laboratory of the Faculty of Chemistry in Lodz.

4.2. Materials

Commercial aldehydes, 2-bromo-3,3,3-trifluoropropene, and 1,1,1-trifluoroacetone were purchased from Sigma-Aldrich. 1,1,3,3-Tetramethyl-8-thia-5,6-diazaspiro[3.4]oct-5-en-2-one (**4b**) [10] and spiro[1,3,4-thiadiazol-2(5*H*),2'-tricyclo[3.3.1.1^{3,7}]decane] (**4c**) [11] were prepared according to known protocols. Tetrahydrofuran (THF) was dried over sodium with benzophenone and freshly distilled prior to its use.

Enones **2** were prepared in a multi-step procedure starting with 2-bromo-3,3,3-trifluoropropene according to a literature protocol [4a].

*(*E*)-4,4,4-Trifluoro-1-phenylbut-2-en-1-one* (**2a**) [4b]. Yield: 80%. Thick yellow oil ([4b]: yellow oil). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.79–6.85 (m, 1H), 7.52–7.55 (m, 3H), 7.63–7.66 (m, 1H), 7.98 (d, J = 8.4 Hz, 2H). ^{19}F NMR (565 MHz, $CDCl_3$): δ –65.0 (dd, J = 6.8, 2.3 Hz, CF_3).

*(*E*)-4,4,4-Trifluoro-1-(4-methoxyphenyl)but-2-en-1-one* (**2b**) [4b]. Yield: 75%. Yellow solid, m.p. 40.0–41.0 °C ([3b]: 41.0–43.0 °C). ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.90 (s, 3H, OCH_3), 6.76–6.82 (m, 1H), 6.98–7.01 (m, 2H), 7.53 (dq, $J_{H,H}$ = 15.6 Hz, $J_{H,F}$ = 1.8), 7.97–7.99 (m, 2H), Hz, 1H). ^{19}F NMR (188 MHz, $CDCl_3$): δ –65.6 (dd, J = 6.4, 2.1 Hz, CF_3).

Enones **3** were prepared from trifluoroacetone and the corresponding aldehyde according to the known procedure [12].

*(*E*)-1,1,1-Trifluoro-4-phenylbut-3-en-2-one* (**3a**). Yield: 40%. Yellow oil ([13]; light yellow oil). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.02 (d, *J* = 16.2 Hz, 1H), 7.44–7.47 (m, 2H), 7.49–7.51 (m, 1H), 7.64 (d, *J* = 7.8 Hz, 2H), 7.97 (d, *J* = 15.6 Hz, 1H). ^{19}F NMR (188 MHz, $CDCl_3$): δ –78.2 (s, CF_3).

*(*E*)-1,1,1-Trifluoro-4-(4-methoxyphenyl)but-3-en-2-one* (**3b**). Yield: 34%. Yellow solid, m.p. 39.0–40.0 °C ([14]: yellow solid, 38.0 °C). ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.88 (s, 3H, OCH_3), 6.89 (d, *J* = 15.6 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.94 (d, *J* = 15.6 Hz, 1H). ^{19}F NMR (188 MHz, $CDCl_3$): δ –78.0 (s, CF_3).

*(*E*)-1,1,1-Trifluoro-4-(furan-2-yl)but-3-en-2-one* (**3c**). Yield: 58%. Yellow oil ([12]: light yellow oil). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.56–6.57 (m, 1H), 6.87–6.89 (m, 2H), 7.58–7.61 (m, 1H), 7.68 (d, *J* = 15.6 Hz, 1H). ^{19}F NMR (188 MHz, $CDCl_3$): δ –78.2 (s, CF_3).

*(*E*)-1,1,1-Trifluoro-4-(thiophen-2-yl)but-3-en-2-one* (**3d**). Yield: 32%. Yellow solid, m.p. 35.0–36.0 °C ([12]: 37.0–38.0 °C). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.78 (d, *J* = 15.6 Hz, 1H), 7.15 (dd, *J* = 4.8, 3.6 Hz, 1H), 7.48 (d, *J* = 3.6 Hz, 1H), 7.58 (d, *J* = 4.8 Hz, 1H), 8.07 (d, *J* = 15.6 Hz, 1H). ^{19}F NMR (188 MHz, $CDCl_3$): δ –78.1 (s, CF_3).

*4.3. Reactions of fluorinated enones **2** and **3** with thiocarbonyl S-methanides – General procedures*

4.3.1. With thiobenzophenone S-methanide

A solution of thiobenzophenone (198 mg, 1 mmol) in dry THF (0.5 ml) was cooled to −78 °C and treated with small portions of an ethereal CH_2N_2 solution until the dark blue color disappeared. A solution of the corresponding enone **2a** or **3c** (1 mmol) in dry THF (0.5 ml) was added at −78 °C. Then, the mixture was allowed to warm slowly to r.t. After 30 min, the solvent was evaporated, and the crude product was purified chromatographically, using as an eluent a mixture of petroleum ether and ethyl acetate (8:2).

4.3.1.1. trans-*[2,2-Diphenyl-4-(trifluoromethyl)tetrahydrothiophen-3-yl](phenyl)methanone (**5a**)*. Yield: 210.0 mg (51%). Colorless crystals, m.p. 128.1–128.6 °C, (P.E.). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.87 (dd, *J* = 12.0, 10.2 Hz, 1H), 3.16 (dd, *J* = 12.0, 7.8 Hz, 1H), 4.15–4.24 (m, 1H), 5.15 (d, *J* = 7.2 Hz, 1H), 6.87–6.93 (m, 3H), 7.02–7.04 (m, 2H), 7.10–7.13 (m, 2H), 7.15–7.17 (m, 1H), 7.19–7.22 (m, 2H), 7.27–7.30 (m, 1H), 7.32–7.34 (m, 2H), 7.46 (d, *J* = 7.4

Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 30.1 (q, $^3J_{C,F}$ = 2.0 Hz, CH_2), 51.6 (q, $^2J_{C,F}$ = 26.7 Hz, C(4)), 55.0 (C(2)), 72.2 (C(3)), 127.1 (q, $^1J_{C,F}$ = 137.1 Hz, CF_3), 127.4, 127.5, 127.6, 128.0, 128.2, 128.3, 128.3, 130.2, 132.7 (15 arom. CH), 138.4, 140.8, 145.2 (3 arom. C), 198.3 (C=O). ^{19}F NMR (188 MHz, $CDCl_3$): δ –68.9 (d, J = 9.0 Hz, CF_3). IR (KBr): ν 2920, 1690, 1597, 1448, 1268, 1163, 1108, 1005, 698 cm^{-1}. Anal. calcd for $C_{24}H_{19}OSF_3$ (412.49): C, 69.87; H, 4.65; S, 7.77; found: C, 69.95; H, 4.88; S, 7.54.

4.3.1.2. (E)-5-[2-(Furan-2-yl)vinyl]-2,2-diphenyl-5-(trifluoromethyl)-1,3-oxathiolane ***(6a)****.* Yield: 237.2 mg (59%). White solid, m.p. 102.5–103.0 °C (purified chromatographically). ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.16 (d, J = 12.0 Hz, 1H), 3.47 (d, J = 12.0 Hz, 1H), 6.06 (d, J = 16.2 Hz, 1H), 6.10 (d, J = 3.6 Hz, 1H), 6.25 (dd, J = 3.6, 1.8 Hz, 1H), 6.48 (d, J = 15.6 Hz, 1H), 6.96–7.05 (m, 2H), 7.15–7.25 (m, 5H), 7.47–7.50 (m, 4 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 39.7 (CH_2), 89.5 (q, $^2J_{C,F}$ = 29.1 Hz, C(5)), 102.8 (C(2)), 110.2, 111.6, 122.3, 123.3 (4 arom. CH), 124.4 (q, $^1J_{C,F}$ = 283.8 Hz, CF_3), 126.7, 127.9, 128.0, 128.2, 128.2, 128.3, 142.8 (9 arom. CH + 2 CH olefin), 143.3, 143.8, 151.5 (3 arom. C). ^{19}F NMR (188 MHz, $CDCl_3$): δ = –76.9 (s, CF_3). IR (KBr): ν 2914, 1665, 1486, 1445, 1318, 1147, 1011, 960, 744 cm^{-1}. HR-ESI-MS: Calcd for $C_{22}H_{18}O_2F_3S$ ($[M + 1]^+$): *m/z* 403.09741; found: *m/z* 403.09757.

4.3.2. With S-methanides of cycloaliphatic thioketones

The corresponding 1,3,4-thiadiazoline **4b** or **4c** (1.1 mmol) and the corresponding chalcon **2a**,**2b** or **3a**–**3d** (1 mmol) was dissolved in dry THF (2 ml). The magnetically stirred mixture was heated in an oil bath (45–50 °C) for ca. 3 h until the gas burette combined with the flask indicated the evolution of stoichiometric amounts of N_2. After removal of the solvent under vacuum, crude products were purified chromatographically, using as an eluent a mixture of petroleum ether and ethyl acetate (8:2).

4.3.2.1. trans-*8-Benzoyl-1,1,3,3-tetramethyl-7-(trifluoromethyl)-5-thiaspiro[3.4]octan-2-one* ***(5b)****.* Yield: 244.2 mg (66%). Colorless crystals, m.p. 114.0–114.5 °C (P.E.). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.13, 1.23, 1.44, 1.57 (4s, 12H, 4 CH_3), 2.84 (dd, J = 12.0, 9.0 Hz, 1H), 3.15 (dd, J = 12.0, 7.8 Hz, 1H), 3.19–3.27 (m, 1H), 4.81 (d, J = 4.2 Hz, 1H), 7.51–7.54 (m, 2H), 7.62–7.64 (m, 1H), 8.03 (d, J = 7.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.5, 22.2, 23.7, 26.0 (4 CH_3), 31.6 (q, $^3J_{C,F}$ = 2.5 Hz, CH_2), 48.7, 62.8, 68.0 (3C_q), 54.4 (q, $^2J_{C,F}$ = 26.8 Hz, C(4)), 71.5 (C(3)), 126.5 (q, $^1J_{C,F}$ = 277.9 Hz, CF_3), 128.6, 129.3, 134.1 (5 arom. CH), 136.5 (1 arom. C), 200.5, 219.4 (2 C=O). ^{19}F NMR (188 MHZ, $CDCl_3$): δ –68.9 (d, J = 8.8 Hz,

CF_3). IR (KBr): ν 2974, 1782, 1679, 1448, 1268, 1157, 1116, 907, 710 cm^{-1}. HR-ESI-MS: Calcd for $C_{19}H_{22}O_2F_3S$ ($[M + 1]^+$): *m/z* 371.12871; found: *m/z* 371.12872. Anal. calcd for $C_{19}H_{19}O_2SF_3$ (370.46): C, 61.60; H, 5.72; S, 8.65; found: C, 61.41; H, 5.74; S, 8.43.

4.3.2.2. trans-*8-(4-Methoxybenzoyl)-1,1,3,3-tetramethyl-7-(trifluoromethyl)-5-thiaspiro[3.4]octan-2-one (**5c**)*. Yield: 335.3 g (83%). White solid, m.p. 82.0–82.7 °C (purified chromatographically). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.08, 1.18, 1.38, 1.52 (4s, 12H, 4 CH_3), 2.77 (dd, *J* = 12.0, 9.0 Hz, 1H), 3.10 (dd, *J* = 12.0, 8.4 Hz, 1H), 3.15–3.22 (m, 1H), 3.84 (s, 3H, OCH_3), 4.71 (d, *J* = 4.2 Hz, 1H), 6.95 (d, *J* = 9.0 Hz, 2H), 7.97 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.3, 22.0, 23.6, 25.7 (4 CH_3), 31.5 (q, $^3J_{C,F}$ = 2.0 Hz, CH_2), 48.2, 62.7, 67.8, (3C), 54.4 (q, $^2J_{C,F}$ = 26.5 Hz, C(4)), 55.6 (OCH_3), 71.3 (C(3)), 114.4 (2 arom CH), 126.6 (q, $^1J_{C,F}$ = 277.9 Hz, CF_3), 129.5, 130.8 (3 arom. CH), 164.3 (1 arom. C), 198.7, 219.4 (2 C=O). ^{19}F NMR (188 MHz, $CDCl_3$): δ –68.9 (d, *J* = 8.8 Hz, CF_3). IR (film): ν 2968, 1780, 1673, 1464, 1258, 1163, 1112, 1027, 736 cm^{-1}. HR-ESI-MS: Calcd for $C_{20}H_{24}O_3F_3S$ ($[M + 1]^+$): *m/z* 401.13928; found: *m/z* 401.13920.

4.3.2.3. trans-(*4-Methoxyphenyl){4'-(trifluoromethyl)-3,4-dihydro-2*H-*spiro[adamantane-2,2'-thiophen]-3-yl}methanone (**5d**)*. Yield: 246.0 mg (60%). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.34–1.36 (m, 2H), 1.59–1.70 (m, 5H), 1.80 (br s, 1H), 1.90–1.94 (m, 2H), 1.99–2.05 (m, 2H), 2.17 (br s, 1H), 2.68–2.70 (m, 1H), 2.98–3.07 (m, 2H), 3.44–3.50 (m, 1H), 3.87 (s, 3H, OCH_3), 4.37 (d, *J* = 6.0 Hz, 1H), 6.96 (d, *J* = 9.0 Hz, 2H), 8.00 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 26.78, 26.79, 29.49, 29.50 (4 CH), 34.2, 35.1, 35.3, 35.4, 37.0, 37.7, 38.4 (7 CH_2), 52.6 (C(2)), 55.6 (OCH_3), 56.2 (q, $^2J_{C,F}$ = 26.1 Hz, C(4)), 71.4 (C(3)), 114.3, 130.7 (4 arom. CH), 126.5 (q, $^1J_{C,F}$ = 277.9 Hz, CF_3), 131.0, 163.9 (2 arom. C), 199.1 (C=O). ^{19}F NMR (188 MHz, $CDCl_3$): δ –69.4 (d, *J* = 9.0 Hz, CF_3). IR (KBr): ν 2911, 1673, 1600, 1511, 1454, 1375, 1258, 1166, 1112, 1030, 840 cm^{-1}. HR-ESI-MS: Calcd for $C_{22}H_{26}O_2F_3S$ ($[M + 1]^+$): *m/z* 411.16001; found: *m/z* 411.15988.

*4.3.2.4. (*E*)-1,1,3,3-Tetramethyl-6-styryl-6-(trifluoromethyl)-5-oxa-8-thiaspiro[3.4]octan-2-one (**6b**)*. Yield: 288.6 mg (78%). White solid, m.p. 51.3–52.0 °C (purified chromatographically). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.22, 1.30, 1.35, 1.40 (4s, 12H, 4 CH_3), 3.19 (d, *J* = 12.0 Hz, 1H), 3.45 (d, *J* = 12.0 Hz, 1H), 6.22 (d, *J* = 16.2 Hz, 1H), 6.92 (d, *J* = 16.2 Hz, 1H), 7.30–7.33 (m, 1H), 7.35–7.39 (m, 2H), 7.41–7.42 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.9, 20.9, 22.5, 22.8 (4 CH_3), 37.6 (CH_2), 65.7, 67.1 (C(1), C(3)), 89.0 (q,

$^{2}J_{C,F}$ = 28.8 Hz, C(6)), 102.8 (C(4)), 123.5 (1 arom. CH), 124.5 (q, $^{1}J_{C,F}$ = 283.6 Hz, CF_3), 127.0, 128.8, 128.9, 135.2 (4 arom. CH + 2 CH olefin), 135.5 (1 arom. C), 219.6 (C=O). ^{19}F NMR (188 MHz, $CDCl_3$): δ –77.0 (s, CF_3). IR (KBr): ν 2977, 1774, 1464, 1299, 1185, 1160, 1068, 1030, 758 cm^{-1}. HR-ESI-MS: Calcd for $C_{19}H_{22}O_2F_3S$ ([M + 1]$^{+}$): *m/z* 371.12871; found: *m/z* 371.12872.

*4.3.2.5. (*E*)-6-(4-Methoxystyryl)-1,1,3,3-tetramethyl-6-(trifluoromethyl)-5-oxa-8-thiaspiro[3.4]octan-2-one (**6c**)*. Yield: 276.0 mg (69%). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.21, 1.29, 1.33, 1.38 (4s, 12H, 4 CH_3), 3.18 (d, *J* = 12.0 Hz, 1H), 3.43 (d, *J* = 12.0 Hz, 1H), 3.82 (s, 3H, OCH_3), 6.07 (d, *J* = 16.2 Hz, 1H), 6.85 (d, *J* = 16.2 Hz, 1H), 6.89 (d, *J* = 9.0 Hz, 2H), 7.35 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.8, 20.9, 22.5, 22.8 (4 CH_3), 37.6 (CH_2), 55.6 (OCH_3), 65.7, 67.0 (C(1), C(3)), 89.1 (q, $^{2}J_{C,F}$ = 28.8 Hz, C(6)), 102.7 (C(4)), 114.4 (2 arom. CH), 124.5 (q, $^{1}J_{C,F}$ = 283.5 Hz, CF_3), 121.2, 128.2, 128.3 (2 arom. CH + 2 CH olefin), 134.6, 160.3 (2 arom. C), 219.8 (C=O). ^{19}F NMR (188 MHz, $CDCl_3$): δ –77.1 (s, CF_3). IR (film): ν 2965, 1784, 1609, 1511, 1464, 1252, 1176, 1071, 818, 698 cm^{-1}. HR-ESI-MS: Calcd for $C_{20}H_{24}O_3F_3S$ ([M + 1]$^{+}$): *m/z* 401.133928; found: *m/z* 401.13941.

*4.3.2.6. (*E*)-1,1,3,3-Tetramethyl-6-[(2-(thiophen-2-yl)vinyl]-6-(trifluoromethyl)-5-oxa-8-thiaspiro[3.4]octan-2-one (**6d**)*. Yield: 327.1 mg (87%). White solid, m.p. 58.0–58.5 °C (purified chromatographically). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.22, 1.28, 1.33, 1.38 (4s, 12H, 4 CH_3), 3.16 (d, *J* = 12.0 Hz, 1H), 3.42 (d, *J* = 12.0 Hz, 1H), 6.03 (d, *J* = 15.6 Hz, 1H), 6.99–7.06 (m, 3H), 7.25 (d, *J* = 5.4 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.8, 20.8, 22.5, 22.7 (4 CH_3), 37.6 (CH_2), 65.7, 67.1 (C(1), C(3)), 88.8 (q, $^{2}J_{C,F}$ = 28.9 Hz, C(6)), 102.9 (C(4)), 122.6 (1 arom. C), 124.3 (q, $^{1}J_{C,F}$ = 283.5 Hz, CF_3), 125.9, 127.6, 127.7, 128.3 (2 arom. CH + 2 CH olefin), 140.4 (1 arom. C), 219.5 (C=O). ^{19}F NMR (188 MHz, $CDCl_3$): δ –77.0 (s, CF_3). IR (KBr): ν 2965, 1771, 1464, 1245, 1169, 1068, 1030, 701 cm^{-1}. HR-ESI-MS: Calcd for $C_{17}H_{20}O_2F_3S_2$ ([M + 1]$^{+}$): *m/z* 377.08513; found: *m/z* 377.08523. Anal. calcd for $C_{17}H_{19}O_2S_2F_3$ (376.48): C, 54.23; H, 5.10; S, 17.03; found: C, 54.23; H, 5.27; S, 17.16.

*4.3.2.7. (*E*)-5'-(4-Methoxystyryl)-5'-(trifluoromethyl)spiro[adamantane-2,2'-[1,3]oxathiolane (**6e**)*. Yield: 270.6 mg (66%). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.65–1.77 (m, 5H), 1.82–1.90 (m, 4H), 2.04–2.11 (m, 2H), 2.20–2.27 (m, 2H), 2.37–2.43 (m,

1H), 3.11, 3.56 (AB, J = 12.0 Hz, 2H), 3.82 (s, 3H, OCH_3), 6.08 (d, J = 15.6 Hz, 1H), 6.87–6.90 (m, 3H), 7.35 (d, J = 9.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 26.7, 26.9 (2 CH), 33.8, 34.9, 37.4, 37.4, 37.6, 37.7 (6 CH_2), 40.0, 40.9 (2 CH), 55.4 (OCH_3), 88.6 (q, $^2J_{C,F}$ = 28.8 Hz, C(5')), 105.2 (C(2')), 114.2, 122.7 (4 arom. CH), 124.6 (q, $^1J_{C,F}$ = 283.3 Hz, CF_3), 128.4 (1 CH olefin), 128.7 (1 arom. C), 133.9 (1 CH olefin), 160.0 (1 arom. C) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ –78.5 (s, CF_3). IR (film): ν 2917, 1603, 1515, 1454, 1249, 1173, 1103, 973, 739 cm^{-1}. HR-ESI-MS: Calcd for $C_{22}H_{26}O_2F_3S$ ($[M + 1]^+$): m/z 411.16001; found: m/z 411.15998.

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